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LONGITUDINAL DECREASES IN FUNCTIONAL CONNECTIVITY AND COGNITIVE DECLINE IN PARKINSON'S DISEASE

ABSTRACT

Objective: To longitudinally evaluate fMRI whole-brain resting-state functional connectivity changes in relation to cognitive decline in Parkinson's disease (PD).

Methods: Resting-state fMRI scans were acquired in 55 PD patients (mean age 65.8 years, SD 6.37; average disease duration 9.24 years, SD 3.96) and 15 matched controls (mean age 64.4 years, SD 8.65). We performed overall (i.e. one whole-brain mean) as well as regional (i.e. for all individual regions of interest) functional connectivity analyses, in which we compared subject groups cross-sectionally. After a follow-up period of three years, 36 PD patients and 12 controls were re-scanned to study functional connectivity changes over time, and correlate the changes in functional connectivity with measures of cognitive and motor function in the PD sample.

Results: We found widespread decreases in resting-state functional connectivity in PD patients in comparison to controls. Subsequent longitudinal analysis revealed that PD patients displayed further decreases in functional connectivity independent of aging effects. These functional connectivity changes were most prominent for posterior parts of the brain and correlated longitudinally with clinical measures of disease progression, especially cognitive decline.

Conclusion: In this longitudinal fMRI study in PD we demonstrated a progressive loss of resting-state functional connectivity for multiple brain regions, especially in posterior parts of the brain. The strong correlation with decreasing cognitive performance supports the pathophysiological role of reduced functional connectivity in cognitive decline and the development of dementia in PD.

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INTRODUCTION

Cognitive dysfunction in Parkinson's disease (PD) displays a poorly understood heterogeneity, with some patients having no impairments at all, while others suffer from rapid cognitive decline ultimately leading to PD-related dementia (PDD).[16-18] A better understanding of the pathophysiological mechanisms underlying cognitive decline in PD could lead to new biomarkers for both prognostic purposes and monitoring of treatment effects in clinical trials.

Preserved cognition in a healthy human brain requires an efficient communication (i.e. functional connectivity) between brain areas.[59,60] In various neurodegenerative diseases, disruptions of resting-state functional connectivity that are related to cognitive dysfunction have been demonstrated using fMRI,[146] but in PD such studies are scarce Only two fMRI studies have addressed the correlation between cognitive function and resting-state functional connectivity in PD so far, and only in selected subgroups of patients.[92,93] Moreover, in previous studies functional connectivity was always analyzed for a subset of brain regions only. At this point, no studies have been performed that assessed whole-brain functional connectivity in PD. Furthermore, what is critically missing in the field, is longitudinal data. It is currently unknown how fMRI resting-state connectivity evolves with disease progression in PD, and whether changes in functional connectivity reflect increasing impairments in cognitive and/or motor function.

In the present longitudinal study we analyzed whole-brain resting-state functional connectivity using fMRI in relation to measures of clinical disease progression in PD. We hypothesized that PD would be associated with decreased functional connectivity and that these decreases would develop in association with progressive functional loss over time.

METHODS

Participants

Participants were part of a longitudinal study cohort of idiopathic PD patients and healthy controls.[81] The fMRI registrations were performed at the first and second follow-up visits, 4 and 7 years after inclusion. fMRI data was available for 59 patients and 15 controls. Four patients had severe movement artifacts during fMRI registration and were excluded, leaving measurements in 55 patients (30 men) and 15 controls (10 men) for analyses.

After a mean interval of 3.12 (SD 0.22) years, a total of 39 out of the 55 PD patients participated in a follow-up evaluation. Two patients had passed away, 3 patients were lost to follow-up and 11 patients consented to neuropsychological evaluation only. Of the remaining patients, 1 had to be excluded due to movement artifacts, while for 2 patients only structural MRI scanning was performed. In the control group 12 subjects returned for a follow-up evaluation, whereas 3 subjects were lost to follow-up. Taken together, longitudinal fMRI analyses were performed in 36 PD patients and 12 controls.

Disease duration was calculated on the basis of the estimated onset of first motor symptoms. Unified Parkinson's Disease Rating Scale motor ratings (UPDRS-III) were obtained in the

"ON" medication state by a trained physician.[100] Global cognitive function was assessed using the Cambridge Cognitive Examination (CAMCOG) scale.[101] Education level was determined using the International Standard Classification of Education (ISCED).[102] The total dose of dopaminomimetics was converted to a so-called levodopa equivalent daily dose (LEDD) using a previously described conversion rate.[125]

Standard protocol approvals, registrations, and patient consents

All participants gave written informed consent to the research protocol, which was approved by the medical ethical committee of the VU University Medical Center. Ethics review criteria conformed to the Helsinki declaration.

MRI data acquisition

All subjects underwent structural 3T-MR scans (GE Signa HDXT, V15M), using a 3D-T1 fast spoiled gradient-echo (FSPGR) sequence (TR 7.8, TE 3.0, TI 450 ms, FA 12, 1.0 x 0.9 x 0.9 mm voxel size). For resting-state fMRI, 202 whole-brain volumes of echo-planar images were acquired, of which the first two were discarded (TR 1800 ms, TE 35 ms, FA 90, 3.3mm isotropic voxel size). MRI scanning was performed while subjects were in the "ON" medication state, as described previously.[125]

fMRI data preprocessing and functional connectivity analysis

fMRI preprocessing used standard FSL protocols, including motion correction, smoothing and high-pass filtering (100s cut-off) and registration to standard space, using the pipeline of MELODIC (part of FSL5; http://fsl.fmrib.ox.ac.uk/fsl/fskwiki).

We assessed functional connectivity between 93 regions of interest (ROIs) covering the entire brain. Cortical ROIs were derived from the automated anatomical labeling (AAL) atlas,[126] whereas subcortical areas were derived from FIRST (also part of FSL5). The AAL regions were kept in standard space, and average time series were extracted after boundary-based registration (BBR, part of FSL5) and nonlinear registration of the preprocessed fMRI data to standard space. Average time series of FIRST regions were extracted in subject space, using an inversed BBR of the FIRST atlas from 3DT1 to fMRI space. This resulted in an individualized atlas featuring 93 ROIs covering all grey matter.

We calculated average time series for each ROI and computed functional connectivity between all pair-wise combinations of brain regions using synchronization likelihood (SL) in BrainWave (version 0.9.101, available from http://home.kpn.nl/stam7883/brainwave.html).[64,147] SL ranges between 0 and 1. An embedding dimension of five data points, a time lag of one data point and a *p*-ref of 0.05 were used in line with previous fMRI work.[77,148] For the initial functional connectivity analysis, we took mean SL per connectivity matrix (i.e. a single whole-brain mean). In subsequent regional analyses, we calculated mean SL values for all individual ROIs, averaging left- and right-sided homologous brain regions, representing a weighted degree for each individual brain region of the atlas.

Statistical analysis

To study differences between patients and controls, we compared the mean whole-brain functional connectivity values from the first fMRI registration between patients (n = 55) and controls (n = 15) with a General Linear Model (GLM) analysis. This analysis included age, sex and education level (ISCED, dichotomized using a median split) as potential confounders. To study the regional distribution of differences in functional connectivity in more detail, we performed a Student *t*-test for each pair of homologous brain regions.

We subsequently analyzed longitudinal changes in mean whole-brain functional connectivity with a GLM analysis for repeated measures with time (2 levels) as repeated measures factor and group (control (n = 12) versus PD (n = 36)) as between subjects factor. Each analysis included age, sex, education level and initial SL value as potential confounders.

Within the group of PD patients, we investigated the longitudinal relationship between mean whole-brain functional connectivity and measures of motor and cognitive function with a Generalized Estimated Equations (GEE) with an exchangeable working correlation matrix.[104] We performed analyses using either UPDRS-III (motor function) or CAMCOG (global cognitive function) as dependent, and functional connectivity values as independent variables. When appropriate, dependent variables were transformed in order to comply with assumptions of normality. Each analysis included sex, age, education level and LEDD as potential confounders.

All analyses were performed using the SPSS Statistics 20.0 software package (IBM Corporation, New York, USA). A significance level of .05 (two-tailed) was applied.

RESULTS

Participant characteristics

Table 1 summarizes the clinical characteristics of all participants included in the current analysis.

At the time of the first fMRI measurement, PD patients had an average disease duration of 9.24 (SD 3.96) years and were moderately affected on motor performance (mean UPDRS-III score 26.6, SD 8.74) and showed slightly lower global cognitive performance (CAMCOG) than controls [$t = 2.63$, $p = .011$].

Longitudinal assessment of clinical parameters revealed a decrease in global cognitive performance (CAMCOG) in PD patients [$t= 2.65$, $p = .012$], but not in controls [$t = 0.252$, $p = .806$]. In addition, PD patients displayed a decrease in motor performance over time [$t = -6.07$, $p < .001$].

Cross-sectional functional connectivity analysis

Mean whole-brain functional connectivity was lower in PD patients (n = 55) when compared to controls (n = 15) [$F(1,68) = 10.2$, $p = .002$]. Post-hoc results with regard to regional distribution patterns revealed this effect to include many brain regions, most prominently parietal, occipital, temporal and premotor regions (Figure 1, Supplementary Table 1).

Table 1 Participant characteristics.

	Cross-sectional analysis		Longitudinal analysis			
			Control (n = 12)		PD (n = 36)	
	Control (n = 15)	PD (n = 55)	Time point 1	Time point 2	Time point 1	Time point 2
Sex (M/F)	10/5	30/25	8/4		22/14	
Age (years)	64.4 (8.65)	65.8 (6.37)	62.9 (8.79)	66.2 (8.77)	65.0 (6.55)	68.1 (6.58)
ISCED (0/1/2/3/4/5/6)	0/0/2/3/1/8/1	0/0/20/15/2/17/1	0/0/2/2/0/8/0		0/0/10/12/2/11/1	
Disease duration (years)	n/a	9.24 (3.96)	n/a	n/a	7.97 (3.57)	11.1 (3.59)
UPDRS-III	2.57 (3.41)	26.6 (8.74)	1.58 (1.62)	1.92 (1.51)	26.5 (7.87)	35.4 (9.64)
LEDD total dose	n/a	792 (529)	n/a	n/a	656 (350)	991 (500)
CAMCOG	99.2 (1.93)	93.8 (7.57)	99.0 (2.00)	98.8 (2.93)	94.7 (6.86)	91.1 (13.7)
Mean connectivity (whole-brain SL value)	0.162 (0.042)w	0.136 (0.022)	0.160 (0.038)	0.151 (0.026)	0.136 (0.018)	0.128 (0.022)

Values are expressed as mean (SD) unless otherwise indicated.
M/F, male/female; ISCED, International Standard Classification of Education; UPDRS-III, Unified Parkinson's Disease Rating Scale motor ratings; LEDD, Levodopa Equivalent Daily Dose; CAMCOG, Cambridge Cognitive Examination; n/a, non-applicable.

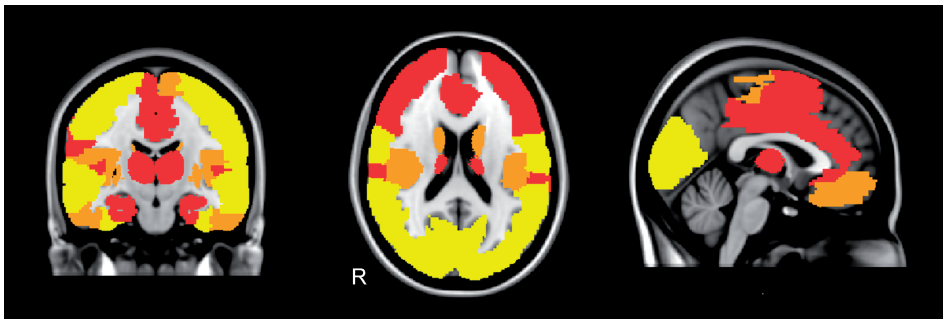

Figure 1 Brain regions having lower resting-stage functional connectivity (expressed as SL value) with all other brain areas in PD patients (n = 55) compared to control subjects (n = 15). Coronal, transverse and sagittal views are shown (X = 91, Y = 109, Z = 91). Legend: yellow: $p < .001$; orange: $p < .01$; red: $p < .05$; independent-samples t-test.

Longitudinal functional connectivity analysis

GLM analysis for repeated measures showed a time x group interaction effect for mean whole-brain functional connectivity [$F(1,45) = 4.52$, $p = .039$], PD patients showing a decrease in functional connectivity over time relative to controls. The strongest decreases in connectivity over time were found in the same regions as in the cross-sectional analysis: occipital, parietal, temporal and premotor regions. Figure 2 and Supplementary Table 2 illustrates the spatial distribution of functional connectivity decreases in PD patients (post-hoc analyses).

After finding prominent decreases in functional connectivity over time for a number of brain regions (Supplementary Table 2), we additionally explored which specific connections most strongly influenced these decreases in average connectivity. To reduce multiple comparison problems, we only investigated one brain structure per lobe, i.e. the ROI showing the strongest decrease in connectivity over time. This resulted in the exploration of the paracentral lobule, superior parietal gyrus, middle occipital gyrus and superior temporal gyrus. Figure 3 and Supplementary Table 3 display the results from these analyses, which point to selective disruptions of the examined seed regions with other brain regions. For example, in the most affected structure, the middle occipital gyrus, functional connections with sensorimotor, frontal, temporal and other occipital regions were most strongly affected.

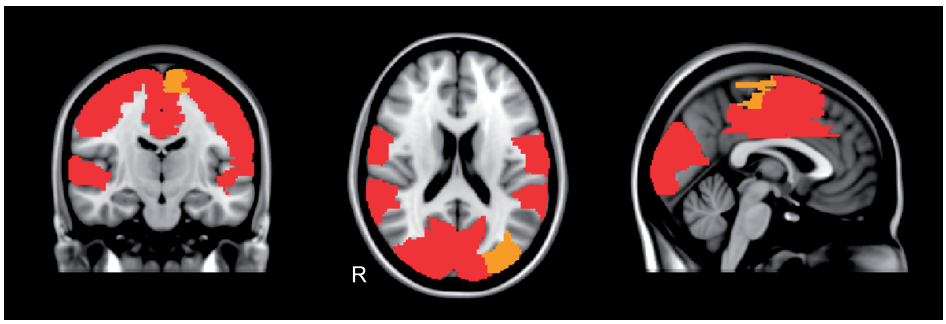

Figure 2 Brain regions showing decreases in connectivity (SL) values in PD patients (n = 36) over time. Coronal, transverse and sagittal views are shown (X = 91, Y = 109, Z = 91). Legend: orange: $p < .01$; red: $p < .05$; paired-samples *t*-test.

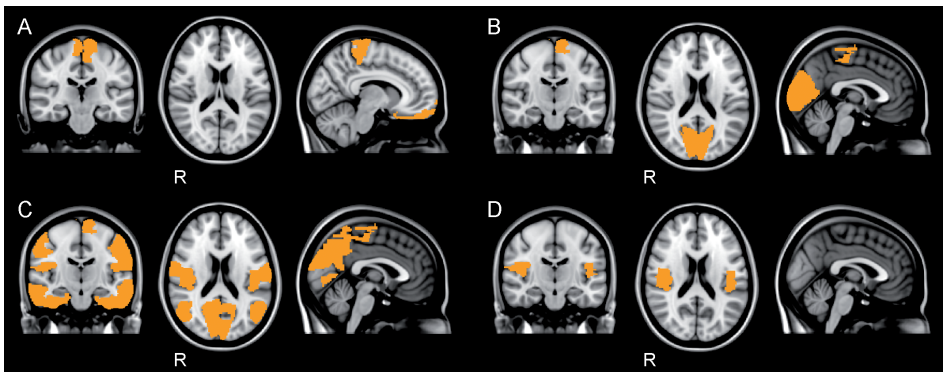

Figure 3 Distribution of reduced functional connectivity with other brain regions (SL, $p < .01$; paired-samples *t*-test) for the paracentral (A), superior parietal (B), middle occipital (C) and superior temporal (D) regions in PD patients (n = 36) over time. Coronal, transverse and sagittal views are shown (X = 91, Y = 109, Z = 91).

Table 2 Longitudinal association between global cognitive performance (CAMCOG) and functional connectivity (SL) in PD patients for the 13 brain regions showing the most significant changes in SL.

Brain region (bilateral)		Brain region (bilateral)	
Inferior frontal gyrus, orbital part	$\beta = .169$ $p = .008$	Middle occipital gyrus	$\beta = .237$ $p < .001$
Supplementary motor area	$\beta = .193$ $p = .003$	Inferior occipital gyrus	$\beta = .207$ $p = .004$
Paracentral lobule	$\beta = .261$ $p < .001$	Calcarine cortex	$\beta = .207$ $p < .001$
Precentral gyrus	$\beta = .198$ $p = .001$	Cuneus	$\beta = .206$ $p = .002$
Postcentral gyrus	$\beta = .184$ $p = .004$	Superior temporal gyrus	$\beta = .184$ $p = .004$
Superior parietal gyrus	$\beta = .242$ $p = .002$	Median (para)cingulate gyrus	$\beta = .185$ $p = .015$
Superior occipital gyrus	$\beta = .238$ $p = .001$		

Beta coefficients are standardized in order to facilitate interpretability.

Relation between functional connectivity and clinical measures

Within the group of PD patients, we assessed the longitudinal relationship between mean whole-brain functional connectivity and CAMCOG (measure of global cognitive function) as well as UPDRS-III (measure of motor function). A longitudinal association was found between worsening CAMCOG performance and lower mean SL [$\beta = .212$; $p = .002$]. There was a trend toward a relationship between UPDRS-III and mean SL: higher UPDRS-III scores, reflecting deteriorating motor function, were associated with lower SL [$\beta = -.188$; $p = .071$].

We then assessed the relative importance of each of the two clinical features by performing supplementary analyses in which we included UPDRS-III and CAMCOG scores, respectively, as a covariate. Worsening CAMCOG test performance remained associated with functional connectivity when controlling for UPDRS-III scores [$\beta = .146$; $p = .036$], whereas the trend-significant relationship between UPDRS-III and functional connectivity was lost when controlling for CAMCOG-performance [$\beta = -.079$; $p = .436$].

Next, we assessed the regional specificity of the relationship between CAMCOG and SL in more detail by performing post-hoc analyses for the 13 brain regions that displayed alterations in SL in both the cross-sectional and longitudinal analysis. As listed in Table 2 decreases in functional connectivity in all of these brain regions correlated with cognitive decline, most prominently so for the paracentral lobule, the superior parietal cortex and occipital brain regions.

DISCUSSION

The present study is the first longitudinal fMRI connectivity study in PD and demonstrates a loss of global resting-state functional connectivity for multiple brain regions in PD, in particular posterior parts of the brain. The decrease in functional connectivity progressively worsens over a period of 3 years and is associated with clinical deterioration, especially cognitive decline.

Previous (cross-sectional) resting-state fMRI connectivity studies in PD have mainly focused on cortico-striatal connectivity in relation to motor symptoms.[90,91] Some studies have included cognitive performance as well, but only within predefined sub-networks, thereby ignoring possible connectivity changes in other parts of the brain. In one of these studies, decreased medial temporal and inferior parietal connectivity within the default mode network (DMN) was associated with cognitive performance in early-stage cognitively unimpaired PD patients.[92] Although this observation suggests that functional disconnection can precede clinically measurable cognitive impairment in PD, it is not clear whether progressive reductions in functional connectivity are actually associated with cognitive decline. We have now demonstrated in a longitudinal study that reductions in functional connectivity over time correlate with progression of cognitive deficits, and therefore may reflect a neural substrate of cognitive decline in PD. In addition, using a whole-brain approach, we were able to demonstrate that the loss of functional connectivity is not restricted to the DMN but involves widespread brain areas.

The loss of functional connectivity in the cross-sectional analysis of our PD sample was widespread but mainly involved the posterior parts of the brain. The longitudinal analysis revealed a smaller number of brain regions with a continuous decrease in functional connectivity in close relation with cognitive decline, in particular multiple occipital regions, the superior temporal gyrus, and also premotor areas. The latter observations is in line with functional imaging studies that have previously implicated the premotor cortex in PD-related cognitive impairment.[149,150] In the present study, the correlation with cognitive decline was strongest for the reductions in functional connectivity of the occipital brain regions, an observation that has not been reported in PD before. Interestingly, post-hoc analyses showed that the decrease in functional connectivity of the occipital regions most strongly involved temporal brain regions, including the parahippocampal regions. This might indicate a disturbance in the ventral stream of information processing, which is strongly related to (visuospatial) cognition, in PD.[151] The dorsal stream appears to be affected in PD as well, since the functional connectivity between parietal and occipital regions was decreased as well. The ventral and dorsal stream areas were also the brain regions that displayed the strongest decrease in connectivity over time. Decreased functional connectivity of occipital brain regions has been reported in PDD, Lewy body dementia and Alzheimer's disease (AD).[94,152,153] Additional studies are needed to explore the specific role of the occipital lobe in cognitive dysfunction in PD in more detail, including its contribution to impairments in visuospatial memory task performance. Future work in PD should also address the predictive ability of functional connectivity markers for conversion to PDD.

Opposed to the strong correlation with cognitive decline, functional connectivity decreases were just modestly related to motor impairments in our study. This may at least partly be explained by the known clinical heterogeneity in the relationship between cognitive impairments and motor disturbances,[135] e.g. some patients with severe motor complications may never develop PDD. Furthermore, the approach of focusing on whole-brain connectivity for each region of interest, might be too diffuse to pick up focused functional connectivity changes specifically limited to the motor system. Cognitive performance, in particular when using a measure of global cognitive function, probably involves a more diffuse array of regions throughout the brain. Future studies should therefore explore the motor network separately, for example by using the primary motor cortex as a seed point for calculating functional connectivity changes. Looking at the most strongly decreased motor connectivity, namely between the primary motor cortex and the superior frontal gyrus, a significant correlation was seen [β = -0.301; p = .027], indicating that a more focused approach could indeed prove more useful in investigating the relationship between the development of motor impairments and changes in functional connectivity in PD.[90]

Previously, we reported changes in resting-state cortico-cortical functional connectivity over time as measured using magnetoencephalography (MEG) and a seed-based approach in our PD cohort. The changes in MEG-derived functional connectivity were correlated with motor and cognitive deterioration.[154] The MEG study involved an earlier phase of the disease, i.e. the four-year period preceding the three-year follow-up period of the present fMRI study. In the earliest clinical stages of PD, we found a loss of resting-state MEG-derived functional connectivity for temporal seed regions with the rest of the brain. With further disease progression, functional connectivity decreased in more widespread cortical areas in close relation to both motor and cognitive deterioration. Interestingly, both the direction (i.e. decreases) and the spatial distribution (i.e. prominent involvement of temporal brain regions) of the MEG-derived changes in functional connectivity are in line with our present fMRI findings, although a direct comparison is difficult as we applied a seed-based rather than a whole-brain approach in the previous MEG study.

In the present fMRI study we did not observe any brain regions with increased connectivity in PD patients. Previous MEG studies have revealed increases in functional connectivity in PD, in particular at early disease stages.[87,154,155] Apparently, increased synchronization might only take place in early stages of the disease, possibly serving as a compensatory mechanism in order to maintain normal functionality. A recent study would seem to support this notion, since the administration of levodopa to drug-naïve patients enhanced functional connectivity as well.[133] From this perspective, a potential explanation for the fact that we did not find increased functional connectivity might thus be that the PD patient group in the present study was at a relatively more advanced disease stage, at which increased functional connectivity mechanisms might have failed already. The same phenomenon is apparent in other neurodegenerative diseases such as multiple sclerosis (MS) and AD.[156-158] The idea of compensatory hyperconnectivity remains to be proven, however, as longitudinal data is still lacking.

The present study has some limitations that need to be addressed. First, several subjects were lost to follow-up, which was partly due to mortality but also to withdrawal, possibly biasing our sample toward patients with slower disease progression. Furthermore, the PD patients in our study were on dopaminergic medication and had their fMRI registrations in the ON state. An influence of dopaminomimetic treatment on our longitudinal analyses can therefore not be excluded. Electrophysiological and fMRI studies confirm that an acute dopaminergic challenge can influence measures of functional connectivity in PD.[90,132,133] Even though the long-term effects of dopaminergic treatment on functional connectivity have not been studied so far, we included LEDD as a covariate in all our longitudinal analyses. Treatment effects on functional connectivity warrant further examination in future studies though.

In summary, this longitudinal fMRI study revealed widespread decreases in resting-state functional connectivity in PD, in particular for the posterior parts of the brain. Over a three-year follow-up period, the decreases in functional connectivity were strongly related to worsening cognitive function. These fMRI data strengthen the idea that a loss of resting-state functional connectivity between brain areas is an important pathophysiological factor in PD-related cognitive decline.

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SUPPLEMENTARY DATA

Supplementary Table 1 Brain regions having lower functional connectivity (synchronization likelihood, SL) values in PD patients compared to control subjects (cross-sectional analysis).

Brain region (bilateral)	SL value controls (n = 15)	SL value PD (n = 55)	*p*-value[#]
Gyrus rectus	0.127 (0.028)	0.110 (0.016)	.003
Olfactory cortex	0.124 (0.015)	0.121 (0.018)	n/s
Superior frontal gyrus, orbital part	0.148 (0.039)	0.123 (0.021)	.002
Superior frontal gyrus, medial orbital part	0.145 (0.035)	0.123 (0.019)	.002
Middle frontal gyrus, orbital part	0.150 (0.050)	0.121 (0.018)	.0008
Inferior frontal gyrus, orbital part	0.162 (0.047)	0.138 (0.024)	.008
Superior frontal gyrus, dorsolateral part	0.163 (0.054)	0.142 (0.029)	.045
Middle frontal gyrus	0.166 (0.060)	0.141 (0.030)	.025
Inferior frontal gyrus, opercular part	0.169 (0.058)	0.141 (0.032)	.019
Inferior frontal gyrus, triangular part	0.162 (0.056)	0.140 (0.031)	.045
Superior frontal gyrus, medial part	0.156 (0.054)	0.138 (0.028)	n/s
Supplementary motor area	0.165 (0.049)	0.143 (0.030)	.032
Paracentral lobule	0.160 (0.050)	0.133 (0.025)	.004
Precentral gyrus	0.179 (0.053)	0.142 (0.030)	.0008
Rolandic operculum	0.187 (0.053)	0.153 (0.030)	.002
Postcentral gyrus	0.176 (0.054)	0.141 (0.028)	.0009
Superior parietal gyrus	0.166 (0.057)	0.133 (0.025)	.002
Inferior parietal gyrus	0.154 (0.054)	0.128 (0.027)	.010
Supramarginal gyrus	0.165 (0.059)	0.137 (0.032)	.016
Angular gyrus	0.140 (0.054)	0.121 (0.027)	n/s
Precuneus	0.168 (0.056)	0.146 (0.033)	n/s
Superior occipital gyrus	0.172 (0.050)	0.138 (0.028)	.001
Middle occipital gyrus	0.180 (0.055)	0.140 (0.029)	.0004
Inferior occipital gyrus	0.170 (0.041)	0.139 (0.025)	.0005
Calcarine cortex	0.184 (0.045)	0.149 (0.030)	.0008
Cuneus	0.177 (0.055)	0.140 (0.028)	.0006
Lingual gyrus	0.187 (0.038)	0.153 (0.029)	.0003
Fusiform gyrus	0.183 (0.043)	0.150 (0.028)	.0008
Heschl's gyrus	0.170 (0.038)	0.148 (0.029)	.015
Superior temporal gyrus	0.195 (0.058)	0.154 (0.033)	.0007
Middle temporal gyrus	0.182 (0.053)	0.142 (0.030)	.0003
Inferior temporal gyrus	0.166 (0.050)	0.140 (0.024)	.006
Temporal pole: superior temporal gyrus	0.155 (0.029)	0.137 (0.021)	.009
Temporal pole: middle temporal gyrus	0.133 (0.031)	0.118 (0.020)	.028
Parahippocampal gyrus	0.153 (0.026)	0.136 (0.020)	.011

Supplementary Table 1 *Continued*.

Brain region (bilateral)	SL value controls (n = 15)	SL value PD (n = 55)	*p*-value[#]
Anterior (para)cingulate gyrus	0.159 (0.032)	0.140 (0.026)	.022
Median (para)cingulate gyrus	0.174 (0.056)	0.149 (0.031)	.027
Posterior cingulate gyrus	0.137 (0.035)	0.128 (0.025)	n/s
Insula	0.180 (0.044)	0.153 (0.030)	.008
Thalamus	0.175 (0.044)	0.150 (0.030)	.012
Caudate nucleus	0.166 (0.058)	0.133 (0.027)	.002
Putamen	0.156 (0.046)	0.129 (0.028)	.006
Globus pallidus	0.145 (0.040)	0.122 (0.020)	.003
Hippocampus	0.158 (0.038)	0.138 (0.024)	.013
Amygdala	0.136 (0.037)	0.119 (0.018)	.011
Nucleus accumbens	0.123 (0.028)	0.111 (0.017)	n/s

SL values are expressed as mean (SD). [#] independent-samples *t*-test; n/s, non-significant.

Supplementary Table 2 Brain regions showing a decrease in functional connectivity (synchronization likelihood, SL) values in PD patients (n = 36) over time (longitudinal analysis).

Brain region (bilateral)	SL value time point 1	SL value time point 2	*p*-value[#]
Gyrus rectus	0.108 (0.014)	0.112 (0.023)	n/s
Olfactory cortex	0.121 (0.019)	0.120 (0.017)	n/s
Superior frontal gyrus, orbital part	0.122 (0.018)	0.116 (0.023)	n/s
Superior frontal gyrus, medial orbital part	0.122 (0.018)	0.121 (0.017)	n/s
Middle frontal gyrus, orbital part	0.120 (0.016)	0.118 (0.025)	n/s
Inferior frontal gyrus, orbital part	0.136 (0.021)	0.127 (0.021)	.035
Superior frontal gyrus, dorsolateral part	0.142 (0.025)	0.133 (0.029)	n/s
Middle frontal gyrus	0.140 (0.027)	0.133 (0.031)	n/s
Inferior frontal gyrus, opercular part	0.139 (0.028)	0.133 (0.032)	n/s
Inferior frontal gyrus, triangular part	0.138 (0.025)	0.131 (0.028)	n/s
Superior frontal gyrus, medial part	0.138 (0.024)	0.133 (0.028)	n/s
Supplementary motor area	0.143 (0.026)	0.130 (0.026)	.011
Paracentral lobule	0.134 (0.023)	0.119 (0.031)	.005
Precentral gyrus	0.143 (0.025)	0.132 (0.028)	.039
Rolandic operculum	0.155 (0.026)	0.146 (0.028)	n/s
Postcentral gyrus	0.141 (0.023)	0.131 (0.026)	.033
Superior parietal gyrus	0.133 (0.020)	0.122 (0.029)	.028
Inferior parietal gyrus	0.126 (0.019)	0.121 (0.026)	n/s
Supramarginal gyrus	0.135 (0.024)	0.126 (0.026)	n/s

Supplementary Table 2 *Continued*.

Brain region (bilateral)	SL value time point 1	SL value time point 2	*p*-value[#]
Angular gyrus	0.118 (0.022)	0.115 (0.025)	n/s
Precuneus	0.146 (0.029)	0.136 (0.032)	n/s
Superior occipital gyrus	0.137 (0.023)	0.125 (0.029)	.013
Middle occipital gyrus	0.139 (0.023)	0.124 (0.031)	.005
Inferior occipital gyrus	0.138 (0.022)	0.127 (0.030)	.036
Calcarine cortex	0.149 (0.027)	0.137 (0.027)	.012
Cuneus	0.140 (0.024)	0.130 (0.029)	.044
Lingual gyrus	0.152 (0.027)	0.143 (0.031)	n/s
Fusiform gyrus	0.150 (0.025)	0.140 (0.031)	n/s
Heschl's gyrus	0.150 (0.025)	0.141 (0.026)	n/s
Superior temporal gyrus	0.155 (0.027)	0.142 (0.031)	.019
Middle temporal gyrus	0.140 (0.024)	0.132 (0.032)	n/s
Inferior temporal gyrus	0.139 (0.022)	0.127 (0.028)	n/s
Temporal pole: superior temporal gyrus	0.138 (0.020)	0.131 (0.019)	n/s
Temporal pole: middle temporal gyrus	0.117 (0.019)	0.110 (0.017)	n/s
Parahippocampal gyrus	0.137 (0.019)	0.132 (0.023)	n/s
Anterior (para)cingulate gyrus	0.141 (0.025)	0.141 (0.021)	n/s
Median (para)cingulate gyrus	0.150 (0.027)	0.137 (0.032)	.043
Posterior cingulate gyrus	0.126 (0.020)	0.120 (0.028)	n/s
Insula	0.155 (0.026)	0.148 (0.028)	n/s
Thalamus	0.149 (0.028)	0.143 (0.032)	n/s
Caudate nucleus	0.132 (0.025)	0.129 (0.029)	n/s
Putamen	0.128 (0.027)	0.121 (0.025)	n/s
Globus pallidus	0.120 (0.017)	0.115 (0.021)	n/s
Hippocampus	0.137 (0.022)	0.130 (0.024)	n/s
Amygdala	0.118 (0.017)	0.116 (0.021)	n/s
Nucleus accumbens	0.110 (0.017)	0.109 (0.020)	n/s

SL values are expressed as mean (SD). [#] paired-samples *t*-test; n/s, non-significant.

Supplementary Table 3 Brain regions showing the most significant ($p < .01$) longitudinal decreases in functional connectivity (SL) with paracentral, superior parietal, middle occipital and superior temporal ROIs in PD patients (n = 36).

ROI (seed)	Connected brain regions	*p*-value
Paracentral lobe	Superior frontal gyrus, orbital part	.001
	Middle frontal gyrus	.007
	Postcentral gyrus	.004
	Superior parietal gyrus	<.001
	Supramarginal gyrus	.009
	Superior occipital gyrus	.006
	Middle occipital gyrus	<.001
	Inferior occipital gyrus	<.001
	Calcarine cortex	<.001
	Cuneus	.004
	Lingual gyrus	<.001
	Fusiform gyrus	.006
	Inferior temporal gyrus	.001
Superior parietal gyrus	Paracentral lobule	<.001
	Calcarine cortex	.001
	Cuneus	.005
	Lingual gyrus	.009
Middle occipital gyrus	Superior frontal gyrus, medial orbital part	.007
	Paracentral lobule	<.001
	Rolandic operculum	.009
	Postcentral gyrus	.003
	Precuneus	.006
	Cuneus	.008
	Lingual gyrus	.003
	Fusiform gyrus	.004
	Middle temporal gyrus	.002
	Inferior temporal gyrus	.008
	Temporal pole: superior temporal gyrus	.007
	Parahippocampal gyrus	.004
Superior temporal gyrus	Rolandic operculum	<.001
	Heschl's gyrus	.009